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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/531,884 | 04/11/2006 | David Haigh | PG4890USW | 4533 |

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| EXAMINER | |
|---|---|
| CHENG, KAREN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1626 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 04/16/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/531,884 | HAIGH ET AL. | |
| | Examiner | Art Unit | |
| | Karen Cheng | 1626 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1 (in part), 3-12 (in part), 21-24 (in part))* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-15* is/are rejected.

7)☒ Claim(s) *1,3-12 and 21-24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

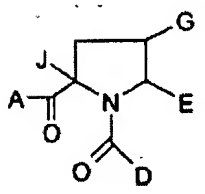
1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-24 are currently pending in the instant application.

### *Election/Restrictions*

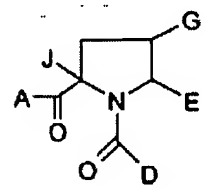
Applicant's election with traverse of Group I, drawn to compounds of formula (Ia)




(Ia)

wherein D is aryl; E is heteroaryl or heterocyclyl; and the other variables are as defined, pharmaceutical formulations, pharmaceutically acceptable salts, solvates, and esters thereof in the reply filed on 04/04/2007 is acknowledged. As stated in the original restriction requirement mailed 3/16/07, the invention as claimed lacks unity of invention since the technical feature fails to define a contribution over the prior art. Thus the restriction is still deemed proper and is maintained.

Since this case is a 371 filing of International Application No. PCT/EP03/11813, filed on 10/22/2003, claims that are directed towards method of use (Claims 13-15) and process of preparation (Claims 22-23) drawn to compound of formula (Ia)



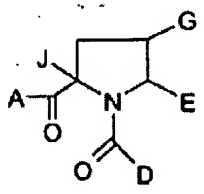

(Ia)

wherein D is aryl; E is heteroaryl or heterocyclyl have been rejoined and fully examined. The election of Group I by applicant has resulted in the followed elected invention.

***Status of the Claims***

**Claims 1-24** are pending in this application. **Claims 16-20** have been cancelled by applicant.

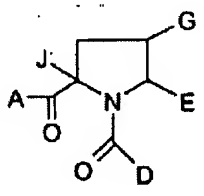
The scope of the invention of the elected subject matter that has been examined are the compounds, pharmaceutical formulations, pharmaceutically acceptable salts, solvates, and esters in **Claims 1-12, 21, and 24**, which share the same core structure shown below:



(Ia)

wherein D is aryl; E is heteroaryl or heterocyclyl.

As a result of the election and corresponding scope of the invention identified supra, the remaining subject matter of **Claims 1-12, 21, and 24** which are drawn to the core structure of



(Ia)

wherein D is heteroaryl; E is hydrogen, $C_{1-6}$alkyl, and aryl is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions.

The scope of the invention of the *non*-elected and *non*-examined subject matter includes the compounds, pharmaceutical formulations, pharmaceutically acceptable salts, solvates, and esters, process of preparation, and methods of use drawn to the compounds described in the paragraph immediately above.

The withdrawn compounds and compositions, which have been withdrawn from consideration as being non-elected subject matter, are patentably distinct inventions

from the process claims currently being examined. Therefore, the subject matter, which has been withdrawn from consideration as being *non*-elected subject matter materially differs in structure and composition from the elected/examined subject matter so that a reference that anticipates the elected/examined subject matter would not render obvious the *non*-elected subject matter. Thus all claims containing compounds falling outside the search strategy of the elected compound and structure shown above are heretofore directed to *non*-elected subject matter and are withdrawn from consideration under 35 U.S.C. § 121 and 37 C.F.R. § 1.142(b). A complete reply to the non-final rejection must include cancellation of non-elected subject matter or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b). if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

***Priority***

The application is a 371 of International Application No. PCT/EP03/11813, filed on 10/22/2003, which claims the benefit of foreign priority under 35 U.S.C. 119, to GB Application No. 0224774.0, filed on 10/24/2002, GB Application No. 0229470.0, filed on 12/18/2002 and GB Application No. 0317141.0, filed on 07/22/2003.

***Information Disclosure Statement***

Applicant's Information Disclosure Statement filed on 04/19/05 has been considered. Please refer to Applicant's copies of the 1449 submitted herewith.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and

8. the level of the skill in the art.

***The nature of the invention***

The nature of the invention is directed to a method of treating or preventing viral infection, such as hepatitis C virus (HCV), comprising administering an effective amount of a compound of Formula (I).

***The state of the prior art and the predictability or lack thereof in the art***

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat or prevent viral infections, such as HCV). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that that contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any preventive regimen on its fact.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The burden of enabling one skilled in the art to prevent viral infections, such as HCV, would be much greater than that of enabling the treatment of viral infections, such as HCV. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of preventing viral infections, such as HCV. Nor is there

any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for preventing viral infections, such as HCV.

Specifically, it is highly unlikely, and the Office would require experimental evidence to support the contention that the claim specified could actually prevent viral infections, such as HCV by simply administering, by any method, a therapeutically active amount of the claim specified agents. The specification fails to enable one of ordinary skill in the art to practice the presently claimed method for preventing viral infections, such as HCV.

"To prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per Webster's II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compositions can be administered to order to have the "prevention" effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with viral infections, such as HCV in general. Moreover, as seen in the prior art, viral infections, such as HCV cannot be prevented by medication due to the uncertainty associated with its transmission (see http://digestive.niddk.nih.gov/ddiseases/pubs/chronichepc/index.htm). Currently, the NIH Consensus Development Conference Panel recommends that therapy for hepatitis C be limited to patients who have histological evidence of progressive disease. Due to the indefinite situations associated with persons afflicted by HCV, indication for therapy

should be reassessed at regular intervals. This showcases the difficulty associated with treatment of the virus, let alone identification of persons who may become afflicted with said virus. Since applicants "preventive" assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits.

According to a NIH conference moderated by Liang, the underlying mechanisms of viral infection, such as hepatitis C, are not well understood. There is currently no vaccine that exists and current therapeutic regimens, which include interferon-α and ribavirin, are problematic and still evolving. Several issues such as the complexity of immune responses against HCV infection, lack of convenient experimental model systems, elucidating the variables and correlates of protective immunity, viral clearance, and disease progression have been and remain to be obstacles in the development of HCV vaccines (p. 303-304). Thus, HCV remains a disease that remains difficult to treat with only limited options available.

**The amount of direction or guidance present and the presence or absence of working examples**

The specification gives test assays that can be used to assess the HCV polymerase activity (see p. 102-105). Although the claimed compounds show activity as inhibitors of *in vitro* HCV RNA-dependent RNA polymerase, there is *in vivo* evidence of the activity of the claimed compounds. Additionally there are no test results showcasing the effects of the compounds on persons afflicted with the HCV virus.

***The breadth of the claims***

The instant breadth of the rejected claims is broader than the disclosure, specifically, the instant claims include prevention and treatment of viral infections, such as HCV but the specification fails to provide evidence of said activity using the claimed compound.

***The quantity or experimentation needed and the level of skill in the art***

It would require undue experimentation of one of ordinary skill in the art to ascertain the effectiveness of the compound in the treatment and prevention of viral infections, such as HCV. Treatment of HCV still remains elusive and unpredictable with only limited treatment regimes available. The lack of understanding of the underlying mechanisms of viral infection, such as hepatitis C, makes the treatment and prevention of hepatitis C difficult. Factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention and unpredictability of preventing and treating viral infections, such as HCV, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in cope with the claims. Absent factual data to the contrary, the amount and level of experimentation needed is undue. Therefore, claims 13-15 are rejected under 35 U.S.C. § 112, 1st paragraph.

***Objections***

Claims 1, 3-12, 21-24 are objected to because of the following informalities: they contain or are dependent on subject matter that has been withdrawn from consideration. Appropriate correction is required.

Claim 4 is missing a period from the end of the claim. Appropriate correction is required.

***Conclusion***

A search was made of the prior art, and the closest art was found in WIPO Pub No. 2003/037895 whereby compounds that have G representing $C_0$alkyl substituted with various substitutents are disclosed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cheng whose telephone number is 571-272-6233. The examiner can normally be reached on M-F, 9AM to 5:30PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Joseph McKane/
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PATENT EXAMINER